

Chapter 20

MEDICAL CHEMICAL DEFENSE ACQUISITION PROGRAMS

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INTRODUCTION

The Department of Defense (DoD) requires medical countermeasures to treat or mitigate illness resulting from exposure to chemical, biological, and radiological warfare agents. While medical chemical defense depends on basic and applied science to gain insight into the pathophysiology, pharmacokinetics, and pharmacodynamics of candidate countermeasures, fielding a medical countermeasure cannot occur until advanced development efforts complete full-rate production and obtain US Food and Drug Administration (FDA) ap-

proval (DoD policy stipulates that military personnel will only receive medical products approved by the FDA. Quad service doctrine, which appears in Army Regulation 40-7, states, "it is the policy of TSG [The Army Surgeon General] that drugs used will be those approved by the FDA and procured from suppliers in the United States."^{1,2} This chapter will briefly describe the US military's organizations responsible for implementing advanced development and will summarize the status of current programs of record.

MEDICAL CHEMICAL ACQUISITION ORGANIZATIONS

The acquisition process may be defined as the process of developing, acquiring, fielding, maintaining, sustaining, and, when necessary, closing out any weapons or protective system in the US military. A drug, vaccine, or medical device used to protect the force against chemical or biological attack is considered a protective system, and medical countermeasures are developed and obtained using what is known as "the acquisition process." The acquisition process includes identifying requirements or capability gaps, identifying potential solutions, and developing and acquiring those solutions, whether the acquisitions are for the development of weapons systems or medical countermeasures.

Chemical and biological defense programs within the DoD are managed by a triad of equal organizations, each of which handles one aspect of the acquisition process. The Joint Requirements Office for Chemical, Biological, Radiological, and Nuclear (CBRN) defense generates and validates requirements from the field, such as the need for a skin decontaminant or for a specific chemical detector. The Defense Threat Reduction Agency, through its joint science and technology office for chemical and biological defense, conducts and supports research and development that seeks to meet these requirements and fill capability gaps. It also maintains a robust science and technology base. This chapter focuses on the third leg of the triad, the organization responsible for the acquisition of medical chemical defense items: the Joint Program Executive Office for Chemical Biological Defense (JPEO-CBD) (Figure 20-1).

In the DoD, all chemical and biological defense acquisition processes fall under the responsibility of the defense acquisition executive (the under secretary of defense for acquisition, technology, and logistics) at the DoD level. Within the DoD, the Army is the executive agent for chemical and biological defense and the assistant secretary of the Army (acquisition, logistics,

and technology) is the Army acquisition executive responsible for managing these programs.

DoD chemical and biological defense acquisition programs are managed by the JPEO-CBD, which is headed by a two-star general, the joint program executive officer. The JPEO-CBD manages \$1.5 billion in acquisition programs, of which approximately 85% are nonmedical programs (boots, masks, gloves, detectors, collective protection, information systems,

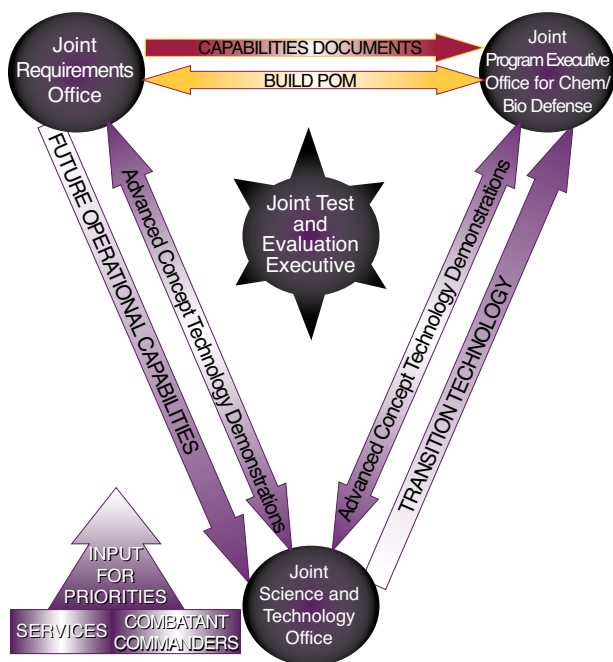


Fig. 20-1. Required capabilities, science and technology, and acquisition responsibilities and interactions.

Bio: biological

Chem: chemical

POM: program objective memorandum

equipment decontamination, etc). The JPEO-CBD is responsible for developing, acquiring, fielding, and supporting chemical and biological defense equipment and medical countermeasures that support the national military strategy.

The JPEO-CBD medical programs are managed by a subordinate organization, the chemical and biological medical systems joint project management office, headquartered at Frederick, Maryland. This office oversees three joint product management components: the joint vaccine acquisition program, the newly established transformational medical technologies initiative, and the medical identification and treatment systems joint product management office (MITS JPMO). The joint vaccine acquisition program is responsible for developing and fielding vaccines and associated products to protect military personnel against biological warfare agents. The transformational medical technologies initiative enables the DoD to protect service members from novel (and potentially genetically engineered)

biological threats through the rapid development of effective therapeutic medical countermeasures, minimizing risks and saving lives. The advanced development of therapeutic and diagnostic products, which includes chemical defense programs, is managed by the MITS JPMO. The mission of the MITS program is to develop and acquire safe, effective, and FDA-approved products for the prophylaxis, treatment, and diagnosis of CBRN warfare agent exposure. The MITS JPMO is also responsible for the critical reagents program, the repository for reagents (probes and primers) and assay kits used in DoD biological detection / diagnostic systems. All MITS medical countermeasures undergoing advanced development for use against CBRN agents are fully integrated into the JPEO-CBD systems of approach to counter threat agents, thereby supporting an integrated diagnostic, prophylactic, and therapeutic capability. MITS medical countermeasures supplement and are compatible with all the equipment developed under JPEO-CBD.

MEDICAL CHEMICAL ACQUISITION PROCESSES AND CONCERNS

The major ground rules for the defense acquisition process are contained in the DoD 5000 series documents.^{3,4} The federal acquisition regulations and supplements also pertain to this process.⁵

Drugs must pass through several phases of clinical trials in order to obtain FDA approval (Figure 20-2). All human research trials conducted in support of the FDA approval process must follow strict FDA regulations and guidelines ("good clinical practices"). In Phase 1 clinical trials, a new drug is first tested in a small group of healthy volunteers (usually 20–80) to evaluate its safety, determine a safe dosage range, identify side effects, and determine how the drug is absorbed, distributed in the body, metabolized, and excreted. In Phase 2 clinical trials, the study drug is given to a larger group of people (usually around several hundred subjects) to evaluate effectiveness and to further evaluate safety. In typical Phase 3 studies, the study drug is given to even larger groups of people, up to several thousand, to confirm its efficacy, monitor side effects, compare it to commonly used treatments, and collect drug safety data. However, Phase 3 studies are not used for the approval of medical chemical countermeasures because it is unethical to test the effectiveness of any drug against chemical warfare agents in people. To overcome this obstacle, the MITS JPMO plans to invoke the "animal rule" (sometimes called "the animal efficacy rule"), which allows for the testing and approval of products when human efficacy clinical trials are not feasible or are unethical,⁶ as DoD accepts this means to licensure. The Phase 2 clinical

trials are used as expanded safety studies for medical chemical countermeasure development and may be divided into multiple arms or studies to address all the regulatory concerns. Phase 4 (post-marketing) studies are conducted after a drug is already approved and on the market. Concurrent with the approval, the FDA may require certain post-marketing studies to delineate and document additional information about a drug's risks, benefits, and optimal use, or it may collect retrospective data on the safety and efficacy of the product if it is ever used. This is especially true for drugs approved under the animal rule. All FDA-required Phase 4 studies are the responsibility of the sponsor, whether that is the US Army Office of The Surgeon General or a system integrator.

Medical CBRN products are developed using a mix of in-house experts and commercial contractors. Within the acquisition process, drug development programs must pass through a series of gates or milestones. A milestone is a point in which a recommendation is made and approval is sought regarding starting or continuing an acquisition program.

Concept Development (Pre-Milestone A Activities)

Drug development decisions must take place earlier in the acquisition process than the typical DoD weapon system development program, requiring earlier user involvement. The DoD 5000 series does not require an analysis of alternatives for drug development efforts because they are not typically major defense

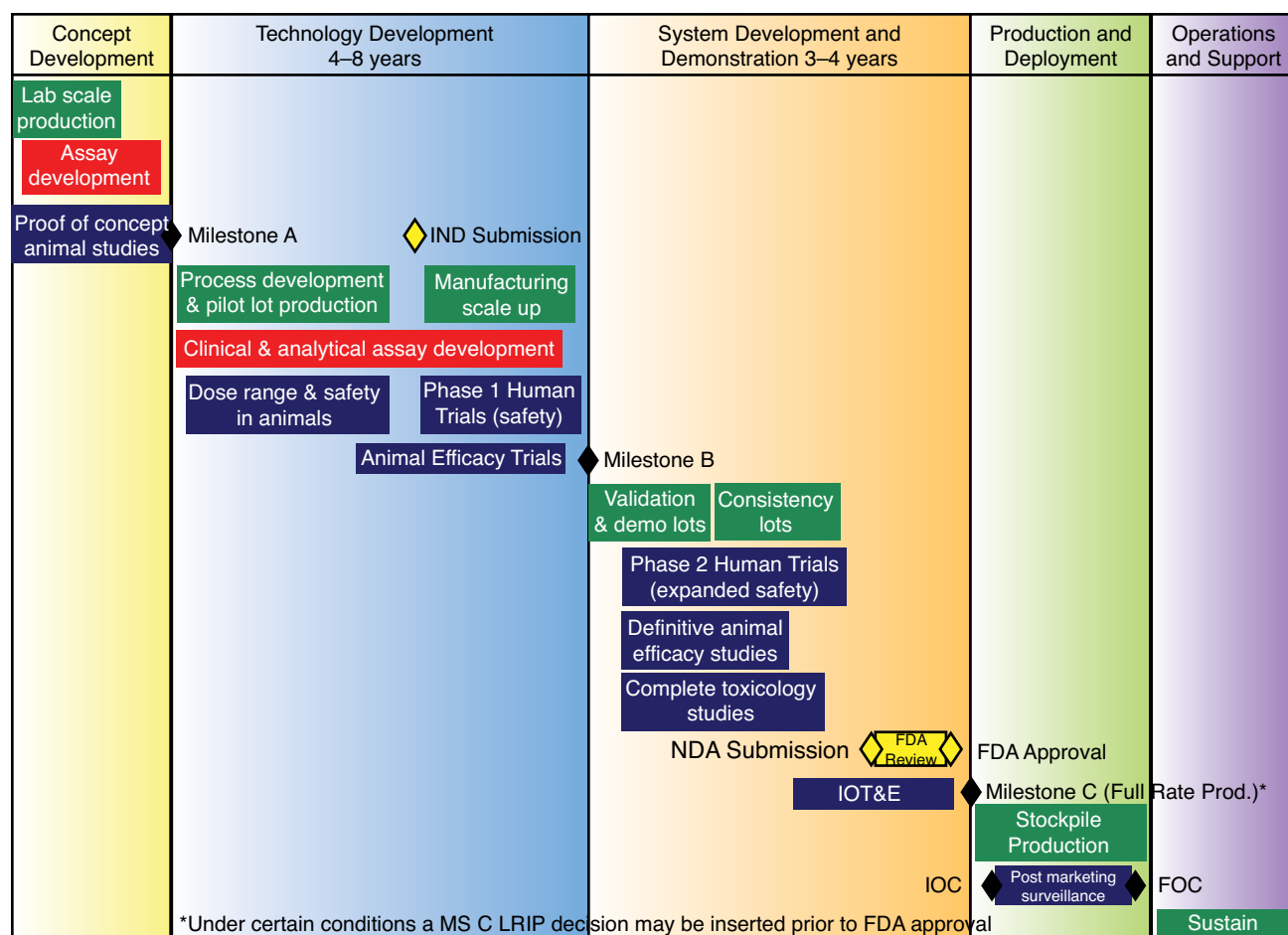


Fig. 20-2. Model for integrating pharmaceutical development, FDA regulatory, and the Department of Defense acquisition processes.

*Under certain conditions, an MS C LRIP decision may be inserted prior to FDA approval.

FDA: Food and Drug Administration

FOC: full operational capability

IND: investigational new drug

IOC: initial operational capability

IOT&E: initial operational test and evaluation

MS C LRIP: milestone C low rate initial production

NDA: new drug application

Prod: production

acquisition programs. However, an analysis addresses all alternatives (eg, prophylactics, pretreatments, therapeutics, and nonmedical countermeasures), considers risk, and performs cost and effectiveness analyses. If development of a drug product is warranted, the technology base assigns personnel, budgets, and facilities and begins basic and applied research. Activities during this phase include assay development and proof of concept animal studies.

The MITS JPMO begins coordinating early with the technology base to gain technical familiarity with potential countermeasure candidates and to ensure

that advanced development funding is aligned appropriately to support a candidate at milestone A. Technology transition agreements are developed with the technology base for each product to ensure a smooth transition to advanced development.

Technology Development

Program management lead shifts from the science and technology base to the MITS JPMO at milestone A. Science and technology and advanced development funds may be used during the technology develop-

ment stage, allowing MITS to engage with the science and technology base early in the process. If multiple candidates are pursued, down-selection criteria are evaluated during technology development and a down-selection recommendation is typically made at milestone B.

Between milestones A and B, the MITS JPMO pursues process development and pilots lot production of candidate drugs under current good manufacturing practices (cGMPs). Required work includes clinical and analytical assay development, dose range and safety studies in animals in accordance with good laboratory practices, investigational new drug (IND) submission to the FDA, and Phase 1 human clinical safety studies compliant with good clinical practices. Emergency use authorization may be prepared and submitted to the FDA for review with, or shortly after, IND submission.

Intellectual property rights are addressed as part of the product transition package (ie, licensure purchase, the need to trace origin to ascertain if it was government funded and, if so, claim government purpose license rights, etc). Intellectual property rights may be a concern for future products, and the MITS JPMO will examine all available options to ensure that products are developed and produced in a manner equitable to the government. Final decision on this approach will be determined by the MITS JPMO.

System Development and Demonstration

During the system development and demonstration phase, the systems integrator, in conjunction with commercial partners, develops validated processes and produces consistency lots and conducts Phase 2 (expanded safety) human studies, definitive animal efficacy studies, and complete toxicology studies. During this phase, the systems integrator files the new drug application or other necessary regulatory documentation and requests FDA submission review. Items carried by service members undergo developmental and initial operational tests and evaluations during this phase. The system development and demonstration phase concludes with FDA approval of the pharmaceutical.

Production and Deployment

As the production and deployment phase begins, products are stockpiled, and post-marketing surveillance is conducted. The MITS JPMO begins investigating post-production support plans and shelf life extension program efforts while monitoring product stability. Initial operating capability for drug develop-

ment is achieved when the FDA approves the product and the contractor can ensure adequate and efficient manufacturing capability. The initial operating capability is calculated as $1/x$ of the troop equivalent doses required for full operating capability, with x being the threshold shelf life. Full operating capability is achieved when the required FDA-approved troop equivalent doses have been produced for the stockpile.

Operations and Support Phase

The MITS JPMO remains responsible for lifecycle management of the approved pharmaceuticals through the operations and support phase of acquisition sustainment, maintaining and safeguarding the industrial capacity to support full production, and addressing regulatory issues such as long-term human safety studies, shelf life extension, and post-marketing surveillance (ie, Phase 4 clinical trials). MITS transfers procurement and logistical management to medical logistics organizations, such as the Defense Supply Center Philadelphia or the US Army Medical Materiel Agency, once initial stockpile quantities are in place. Funding for maintaining the stockpile in the operations and support phase is the responsibility of the individual services.

Acquisition Manufacturing Strategy

The technology base develops a laboratory-scale manufacturing process that is capable of producing only small quantities of drug product. This process must be transferred to a manufacturing facility that adheres to cGMPs and development efforts initiated to ensure technology can be duplicated or new processes pursued. One or more small cGMP pilot lots are manufactured for use in the Phase 1 and 2 clinical trials and animal toxicity studies. Scaling up the manufacturing process, rather than producing additional lots at the smaller scale, can result in significant cost and schedule savings. The manufacturing process is validated and consistency lots are manufactured concurrent with Phase 2 trials. After FDA approval, replenishment lots are produced to meet requirements, depending on the shelf life approved by the FDA for each product.

Acquisition Test and Evaluation Strategy

The acquisition of medical CBRN defense products for the DoD is tailored to comply with the requirements of both the DoD and the FDA. In a memorandum dated November 21, 2003, the deputy under secretary of the Army required every chemical or biological defense

program, except IND programs, to have a test and evaluation master plan. IND applications accepted by the FDA must satisfy the test and evaluation master plan requirement for drug development programs and provide authority for testing drug products in human volunteers in accordance with Army Regulation 73-1, *Test and Evaluation Policy*. For soldier-carried items, a modified test and evaluation master plan must be executed to ensure compatibility and survivability of the item and its packaging.

Acquisition Business and Contracting Strategy

The MITS JPMO is responsible for the advanced development of medical CBRN drugs. Commercial, off-the-shelf medical products are normally procured through the medical logistics system or through procurement contracts issued directly to the vendor by the servicing government contract office.

If the MITS JPMO pursues product development, it will seek a contractor to serve as the systems integrator, generally releasing a request for proposal and making it available to full and open competition. If no commercial entity is identified to serve as the systems integrator, MITS will serve as the systems integrator for products transitioning from the technology base up to milestone B, at which point a contractor will be selected.

MITs streamlines acquisition by providing a performance-based statement of objectives (in lieu of a detailed statement of work) in the request for proposal, which might impede competition because of numerous specific requirements. A performance-integrated product team, consisting of representatives from MITS, the Joint Requirements Office, and the appropriate Joint Science and Technology Office capability area program office, oversees contractor performance in accordance with best commercial and government practices. Ad-hoc members are drawn from MITS, the US Army Medical Research and Materiel Command, the test and evaluation community, JPEO-CBD, the Office of the Secretary of Defense and other DoD offices, the Department of Health Human Services and other federal agencies, the technology base, or the logistics community, as needed. Working performance-integrated product teams are formed to address issues focused on a specific requirements area pertaining to the product.

The DoD, sponsored by the US Army Office of The Surgeon General, currently holds the INDs and approvals of medical chemical defense products. The decision to allow a commercial contractor to hold the IND and drug approval for future products is made on a case-by-case basis. An approach is recommended

as soon as possible, even as early as milestone A. The recommendation is based on several factors, including commercial interest, interagency discussions, and intellectual property rights.

Specific Concerns in Medical Chemical Defense

The biggest challenge in medical acquisition within the DoD is that medical development is dictated by the process of obtaining FDA approval. In this chapter, the phrase “FDA approval” broadly applies to drugs, biologics, and medical devices. In its strictest sense, the term “approval” is usually reserved for drugs, while “licensure” is used for biologics and “clearance” is used for medical devices. All drugs, vaccines, or medical devices intended for use on or in service members are regulated by the FDA. In a pharmaceutical, vaccine, or medical device company, the steps required for obtaining FDA approval drive the drug development process. Within the DoD, however, medical acquisition is embedded within the acquisition model, which was designed around planes, ships, and tanks. Thus, the challenge is to match the DoD acquisition model with the process of pharmaceutical development and FDA approval, so decisions that would be made later in the process in nonmedical military acquisition programs must be made far earlier in the medical realm, allowing INDs to be submitted to the FDA on a timely basis. The challenge, specifically for the MITS JPMO, is to integrate the FDA regulatory and DoD acquisition processes.

The need for FDA approval of any fielded product may be self-evident but deserves comment nonetheless. In civilian medicine, any licensed physician may prescribe any FDA-licensed product, whether the product is for the licensed indication or for some other symptom. Countless examples exist of “off-label” medications approved for one indication but now primarily used for others. In acute nerve agent poisoning, however, patients must be treated far forward by buddies or medics and not by licensed physicians. In that case, only an FDA-approved product used on-label can legally be given by the buddy or medic. Until full FDA approval for this indication in 2003, the use of pyridostigmine bromide as a pretreatment against soman poisoning was an off-label use, notwithstanding the over 50 years of experience using it for patients with myasthenia gravis. Until the FDA approved pyridostigmine bromide specifically for soman intoxication pretreatment, the DoD planned to institute a process of informed consent for each service member, meaning each had the right to decline to use the drug for that purpose. Once FDA approval was obtained, however, the DoD acquired the right to order its service members

to take the drug.

Peculiarities of medical chemical drug development create even greater challenges. For example, unlike a naturally occurring microbial illness, the disorders caused by chemical warfare agents are not expected to occur in the general population on a regular basis. Thus, the standard model for testing drugs in clinical trials is insufficient because exposing volunteers to chemical warfare agents is unethical. Consequently, the usual route for testing and demonstrating both safety and efficacy of medical countermeasures in humans is not feasible. In 2002 the FDA recognized this problem, unique to chemical and biological warfare countermeasure development, and released the animal rule. As a result, the FDA will consider approving medical chemical, biological, and radiological countermeasures when human safety data and sufficient animal efficacy data are presented without definitive human efficacy data. This rule allows for the submission of well-controlled animal efficacy data, in multiple species, to demonstrate that the product is likely to have clinical benefits in humans, in lieu of definitive human efficacy studies. So far, only two products have been fully licensed by the FDA under this rule, pyridostigmine bromide for pretreatment against soman poisoning, approved in 2003 (see Chapter 5, Nerve Agents), and hydroxocobalamin, approved as an antidote for cyanide poisoning in 2007. So far, the animal rule has only been used for products specifically intended for medical chemical defense, but several products in advanced development include plans to use the animal rule in their regulatory

development strategies as necessary.

Another challenge encountered during medical chemical drug development concerns the specific indications for which a drug is used in medical chemical defense. Although all of the classical organophosphorus nerve agents work by inhibiting the enzyme acetylcholinesterase, under a narrow reading of the statute, to obtain FDA approval for all potentially encountered battlefield nerve agents, DoD would have to obtain FDA approval against each individual nerve agent. Instead, DoD plans to seek FDA approval for a whole class of acetylcholinesterase inhibitors. As mentioned earlier, pyridostigmine bromide carries pretreatment licensed indication only against soman. This issue is a matter of present discussion with the FDA, but remains unresolved.

Specific manufacturing challenges exist and are also of concern to the FDA and the advanced developer. Stereoisomers (chiral forms of molecules) and polymorphisms (multiple crystal forms of the same molecules) must always be considered and the licensed compound's purity must be ensured. Impurities must be removed or minimized and characterized. A specific medical chemical defense challenge is that drugs must often be formulated for compatibility and bioavailability in an autoinjector delivery system, which is rarely used in other drug development programs. This challenge was met by the antidote treatment nerve agent autoinjector (ATNAA) program, in which the actual dose of atropine in the autoinjector had to be modified.

STATUS OF ACQUISITION PROGRAMS OF RECORD

The programs of record in medical chemical defense within the DoD may be divided into three categories: lifecycle management products (fielded), sustainment programs (FDA-approved products; post-marketing or Phase 4 trials required), and advanced development programs (products not yet fielded).⁵

Lifecycle Management Products

Several products have gained full FDA approval for an intended indication and are presently fielded. The Mark I (Meridian Medical Technologies Inc, Bristol, Tenn) nerve agent antidote kit descends from the AtroPen (Meridian Medical Technologies Inc), an atropine autoinjector, first developed in the 1950s for nerve agent and insecticide poisoning (see Chapter 5, Nerve Agents). The Mark I kit consists of an atropine autoinjector and a second autoinjector containing 2-pralidoxime chloride (2-PAM Cl). It achieved FDA approval in the 1980s and is the mainstay of fielded

nerve agent antidotes. As such, it has a large hold on the civilian and military markets. The Mark I is being phased out and replaced with the ATNAA.

The convulsant antidote nerve agent (CANA) is an autoinjector for intramuscular administration of 10 mg of diazepam. The CANA is used as an anticonvulsant for nerve agent poisoning and was FDA approved in December 1990. It is the only approved treatment specifically for nerve-agent-induced seizures. The autoinjector has a unique shape that allows a medic or buddy to distinguish it from Mark I, ATNAA, atropine-only, and other autoinjectors in a situation of light discipline.

The medical aerosolized nerve agent antidote (MANAA) is an aerosol inhaler that contains atropine and was developed as a follow-on treatment for nerve agent casualties under medical supervision. It is intended for use after administration of either Mark I or ATNAA and after the casualty has been decontaminated and transferred to a clean environment

where protective suits and masks are not required. MANAA was intended to allow a medic to supervise a group of casualties who were capable of assisting with their own care. Theoretically, MANAA could free up medical personnel to treat more severely poisoned or injured casualties in a mass casualty situation. No other aerosolized treatment for nerve agent poisoning has been licensed by the FDA. MANAA was approved by the FDA in 1990.

MANAA is approaching the end of its shelf life. The manufacturer no longer maintains the cGMP manufacturing line required to produce MANAA. Under the Montreal Protocol, an international treaty created to phase out ozone-depleting substances, aerosolized products such as MANAA must be discontinued because they contain chlorofluorocarbons. A congressionally-funded program for a dry powder inhaler atropine (DPIA) seeks to develop a product that will replace the MANAA. DPIA is being developed jointly by a team that includes MicroDose Technologies, Inc, the University of Pittsburgh, and the MITS JPMO. DPIA is anticipated to be FDA approved in 2009, with fielding anticipated the following year.

ATNAA is a product developed to replace and improve upon the Mark I. It is a dual-chambered autoinjector that delivers 2.1 mg atropine (as compared to the 2 mg atropine in the Mark I) and 600 mg 2-PAM Cl through a single needle. ATNAA was approved by the FDA in January 2002 and fielding began in 2003. ATNAA delivers antidotes faster than Mark I because it uses a single autoinjector rather than two, cutting the time needed to administer life-saving treatment to a nerve agent casualty in half. ATNAA is also smaller, easier to use, and less expensive than the Mark I.

Sustainment Programs

Other products carry FDA approval but require Phase 4 (post-marketing) studies as mandated by the FDA. For example, the Skin Exposure Reduction Paste Against Chemical Warfare Agents (SERPACWA; Fisher Bioservices, Rockville, Md) is a perfluorohydrocarbon-based barrier cream intended to pretreat vulnerable skin areas (such as the groin, neck, wrists, armpits, waistline, and boot tops) prior to donning protective overgarments. SERPACWA provides a passive barrier that protects the skin from liquid chemical agent exposure for over 8 hours. While SERPACWA is meant to be used in conjunction with mission-oriented protective posture, some Special Forces units have inquired about its use without full mission-oriented protective posture protection. The FDA approved SERPACWA in February 2000 and the US Army has purchased initial quantities. SERPACWA also protects against many

natural toxins as well, including poison ivy, suggesting a possible use in civilian medicine. However, SERPACWA is currently only approved for military use.

Studies are ongoing to determine the compatibility of SERPACWA with the M291 skin decontamination kit, a pouch containing six individual decontamination packets that can provide a total of three complete skin decontaminations. SERPACWA currently has an FDA-approved, 3-year shelf life, and is included in the FDA/DoD shelf life extension program.

Another FDA-approved product awaiting Phase 4 trials is soman nerve agent pretreatment pyridostigmine, which is distributed as 30 mg pyridostigmine bromide tablets. In February 2003, this pretreatment became the first drug to be approved by the FDA via the animal rule.

The FDA has mandated the following post-marketing studies for this product:

- a human serum study to correlate dose response between pyridostigmine bromide blood levels and red cell acetylcholinesterase inhibition;
- a guinea pig study to correlate blood pyridostigmine bromide levels, red cell acetylcholinesterase inhibition, tissue acetylcholinesterase inhibition, and the direct effects upon the diaphragm;
- a nonhuman primate study to look at the same questions as in the guinea pig; and
- an in vitro human intercostal muscle study to determine if pretreatment can provide partial protection to soman exposure of the muscle.

The first two studies are complete, the remaining studies are ongoing.

Products in Advanced Development

The joint service personnel/skin decontamination system (JSPDS) program is tasked with developing an improved skin decontamination capability through open competition between commercially available products. The current skin decontamination kit, M291, which has been fielded since 1989, is based on the Ambergard resin (Rohm and Haas, LLC, Philadelphia, Pa) that adsorbs and slowly detoxifies chemical agents. The JSPDS program is under the purview of the Joint Project Management Office for Decontamination, with medical consultation from MITS JPMO. The Joint Project Management Office for Decontamination competitively chose Reactive Skin Decontamination Lotion (RSDL; E-Z-EM, Inc, Lake Success, NY), developed by the Canadian Department of National Defence under

a license from the Canadian Commercial Corporation, for evaluation against the JSPDS requirements. RSDL neutralizes and removes both vesicants and nerve agents from the skin. Clinical studies completed in 2006 show that RSDL can be safely used under ambient and heat-stressed conditions. Results from limited animal studies suggest that RSDL may be safely used around wounds, which is in contrast to M291, which cannot be used around wounds.

With an anticipated shortage of Ambergard resin in 2000, the JSPDS program planned to develop RSDL as a replacement for the M291 system and compared RSDL with M291 under a DoD foreign comparative testing program, aiming to obtain FDA approval. The FDA approved RSDL in 2003. The fielding decision was expected in 2007, but as of early December, it had not been made. RSDL costs considerably more than M291. Very recently, Rohm and Haas has resumed production of Ambergard, which will require considering the pros and cons of moving to field RSDL as a substitute, continuing to field M291, or using a combination of the two.

The advanced anticonvulsant system is the acquisition program that seeks to develop midazolam in an autoinjector as a replacement for the CANA, which contains diazepam, to treat nerve-agent-induced seizures (see Chapter 5, Nerve Agents). Midazolam is presently approved for other indications and has been marketed for many years as a central nervous system depressant, but it does not carry FDA approval as an anticonvulsant, despite being used as such in many clinical contexts in an off-label fashion. Consequently, the focus of the advanced anticonvulsant system program is to obtain FDA approval for midazolam against nerve-agent-induced seizures. Midazolam's action is onset faster and lasts longer than that of diazepam. There may also be less chance of respiratory depression with midazolam. If fully developed, midazolam will be an autoinjector product like CANA.

The regulatory developmental strategy for obtaining FDA approval for midazolam as an advanced anticonvulsant system includes using the animal rule. An IND application was submitted to the FDA in April 2006. The Phase 1 clinical study is complete. Developmental concerns with midazolam include the following:

- respiratory depression (although probably less than with diazepam),
- the number of nerve agents for which on-label indication would be sought,
- Phase 2 clinical studies including drug-to-drug interactions, if any, and
- any postmarketing studies the FDA may mandate.

Approval is planned no later than 2011.

The improved nerve agent treatment system program addresses the shortcomings of 2-PAM Cl as a reactivator of acetylcholinesterase. The program has two goals. The first is to expand the on-label indications for pyridostigmine bromide against more nerve agents than it is presently approved to treat. The second aim is to develop a new oxime, MMB4 dimethanesulfonate, to replace 2-PAM Cl. MMB4 was selected because its spectrum of action is broader than that of 2-PAM Cl for reactivating nerve-agent-inhibited acetylcholinesterase.

MMB4 is not FDA approved in the United States for several reasons. For example, one reason is that many compound polymorphs are present in MMB4, causing stability and solubility concerns. Other reasons are that the number of nerve agents for which an indication for MMB4 must be determined before approval can be granted, and the design of definitive animal studies (including determining the number of agents, animals, and comparisons against 2-PAM Cl that will be needed) must be designed. The regulatory development strategy for MMB4 includes requesting the use of the animal rule. An IND application submission is anticipated in 2008, followed by approval in 2013. Postmarketing studies may also be required by the FDA.

The bioscavenger program (see Chapter 7, Nerve Agent Bioscavenger: Development of a New Approach to Protect Against Organophosphorus Exposure) consists of three separate increments. Increment I is the plasma-derived human butyrylcholinesterase, which carries few immune potential concerns because it is a human product derived from human serum. The availability of this product is limited by the supply of human serum that is suitable for manufacture of a licensed product for use in humans. In addition, manufacture of plasma-derived human butyrylcholinesterase is extremely expensive. Therefore, Increment I is considered an interim solution to the bioscavenger problem from the acquisition standpoint. The DoD will develop this product through Phase 1 clinical trials, with completion scheduled for 2007. The contractor to the DoD is Dynport Vaccine Company, with Baxter Healthcare Corporation as subcontractor; Baxter Healthcare is the sponsor of the IND application, which was submitted to the FDA in May 2006.

The Increment II program will develop a product that is more easily and economically produced than Increment I. Increment II will mitigate technical risk by transitioning two different technologies (a recombinant human butyrylcholinesterase raised in a transgenic animal and a synthetic small molecule with bioscavenging activity) through Phase 1 clinical trials. Efforts

will be tailored to each technology for evaluating and maturing that technology (recombinant or small molecule) and only one technology will be selected for acquisition program initiation at milestone B. The selected product will solve the problem of short supply and consequent expense that Increment I poses,

but may create challenging safety concerns. An FDA-approved product is anticipated no earlier than 2013.

Increment III is envisioned as a catalytic scavenger of nerve agent, likely to be developed with site-directed mutagenesis. No candidate is yet ready for advanced development.

SUMMARY

Good science is not enough to protect service members against the threat of chemical warfare agents. A product must be developed and approved for human use by the FDA, doctrinally on-label for the envisioned use. It must also be manufactured, stockpiled, and delivered, and the user, whether a physician or the casualty's buddy, must know how to use it, which may require extensive training. Finally, the product must be managed throughout its lifecycle and closed out if deemed necessary or if a superior product replaces it.

These tasks all fall under the medical chemical acquisition mission. The average licensed product costs \$400 to \$800 million⁷⁻⁹ and the vast majority, 80% to 90% by some estimates, of products in development fail to obtain full licensure. While the clinician or medical planner need not know the details of the acquisition mission or of its constituent parts, it is vital to recognize that this process is time- and resource-consuming, yet necessary if military personnel are to have proper countermeasures available should the need arise.

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